CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
PHORATE (THIMET)

Chemical Code # 000478, Tolerance # 00206
SB 950 # 046

February 24, 1987
Revised 5/5/88; 8/28/89; 1/3/90; 7/1/92; 3/25/96

I. DATA GAP STATUS

Combined (onco + chronic) rat:	No data gap, no adverse effect
Chronic dog:	No data gap, no adverse effects
Onco mouse:	No data gap, no adverse effect
Repro rat:	No data gap, no adverse effect
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox:	No data gap, no adverse effect

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name T960325
Revised by: D. Shimer and J. Gee, 3/88; G. Chernoff, 8/89, 1/90; Gee, 7/1/92; M. Silva, 3/25/96.

Record numbers through volume 206-054 listed by the Pesticide Registration Library have been rectified with those listed in the Toxicology Summary.
All record numbers through 093218 were examined.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY SUMMARY

COMBINED (ONCO + CHRONIC) RAT

**024 to 027 034568, -69, -77 and -78 "24-Month Chronic Toxicity and Potential Carcinogenicity Study in Rats; Phorate, Final Report." (Litton Bionetics, 5/81, No. 20821.) Phorate, 84.5%; fed in the diet at 0, 1, 3 or 6 ppm, 50/sex/group Sprague-Dawley rats; sys NOEL = 3 ppm (decreased weight gain), ChE NOEL < 1 ppm; no adverse effect identified. ACCEPTABLE for onco study, with variances for chronic. J. Schreider, 3/26/85 and J. Remsen (Gee), 11/1/85

EPA 1-liner: Minimum for oncogenicity, supplementary for chronic toxicity. Oncogenic NOEL > 6 ppm; NOEL < 1 ppm (LDT) (plasma cholinesterase inhibited).

004 928011, -012 and -013 Incomplete version of 34568, -569, -577 and -578.

CHRONIC DOG

**037 058864 "One-Year Oral Toxicity Study in Purebred Beagle Dogs with AC 35,024." (Tegeris Laboratories Inc., 2-20-87) AC 35,024, lot 4870-110, 92.1%, was given to Beagle dogs daily in capsules for one year at 0, 5, 10, 50 or 250 ug/kg/day. Control had 8/sex, treated groups had 6/sex. All required parameters were examined. Systemic NOEL = 50 ug/kg/day, slight tremors, male body weights lower than control though not significant, reduced cholinesterase levels in plasma, RBC and brain. ACCEPTABLE. No adverse effects. Shimer, and Gee, 3/1/88.

ONCOGENICITY, MOUSE

**022 and 023 034570 and -75 "18-Month Chronic Toxicity and Potential Carcinogenicity Study in Mice; Phorate: Final Report." (Litton Bionetics, 1/81, No. 20820.) Phorate, 84.5%, fed to 50/sex/group, Swiss albino mice, at 0, 1, 3 or 6 ppm for 18 months; NOEL = 3ppm (slightly lower body weight - 5%); no hematology. ACCEPTABLE. No oncogenic effect reported. J. Schreider, 3/27/85 and J. Gee, 11/1/85.

EPA 1-liner: Minimum. Oncogenic NOEL > 6 ppm (HDT).

017 016430, 016840, -41 Summary of 34570 and 34575.

004 928014 Incomplete version of 34570 and 34575.

REPRODUCTION, RODENT

**206-054 093218, "A Two-Generation (Two Litters) Reproduction Study with AC 35,024 to Rats", (R.E. Schroeder, Bio/dynamics, Laboratory Report No. 88-3350, sponsor report no. 971-88-156, 9/23/91). AC 35,024 (Phorate), purity 92.1%, was fed in the diet at nominal concentrations of 0, 1, 2, 4, and 6 ppm for two successive generations (2 litters/generation) to CD* (Sprague-Dawley derived) rats. Group size was 25/sex for all groups except for the 6 ppm group of the F1 generation, which had 30/sex. Parental NOEL = 2 ppm, based on occasional tremors in 4 ppm females, and on exophthalmos in one 4 ppm female. Apparent cholinesterase inhibition NOEL = 2 ppm (brain and plasma ChE inhibition in 4 ppm females). Reproductive NOEL = 2 ppm, based on reduced pup weights, and increased F2a pup mortality at 4 and 6 ppm. Common findings in 6 ppm parental rats included reduced body weights of P1 females and F1 males and females; tremors in the above groups (particularly in young rats and in lactating females); exophthalmos; corneal scarring, anterior

synechia, and related symptoms in both sexes of F1 rats. Survival was decreased for high dose F1 females. Brain ChE was inhibited by 40% in 6 ppm F1 males, and by 59% and 83% in 4 ppm and 6 ppm F1 females, respectively. Pup body weights and pup survival were significantly reduced at 6 ppm in all breeding periods. **Acceptable**. **No adverse effects**: (no reproductive effects below dose levels which caused clinical signs of cholinesterase inhibition). (Kishiyama and Gee, 6/30/92).

028 034576 "Thimet Systemic Insecticide: Successive Generation Studies with Mice." (American Cyanamid, 12/23/65.) Phorate, 98.4%, Lot AC-841-56A; fed to 8 males and 16 females per group at 0, 0.6, 1.5 or 3.0 ppm, three generations, two litters per generation; UNACCEPTABLE (dose selection with no evidence of clinical toxicity, inadequate histopathology). Initial review noted an inadequate number of animals but since there were two litters per generation, overall an acceptable number of pups/litters were available for observation. Parental and reproduction NOEL > 3 ppm. Not upgradeable. J. Gee, 11/1/85 and 3/2/88.

EPA: No further data required [as of 1984]. NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/18/89) notes EPA classification as "Core Minimum".

006 034040 Summary of 034576.

005 928033 (American Cyanamid, 1965) Summary only of 034576. J. Schreider, 3/27/85.

TERATOLOGY, RAT

** 052 089065, "An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Definitive Study with AC 35,024 in Rats", (E. A. Lochry, Argus Research Laboratories, Inc., Lab Protocol 101-012, 10/23/90). AC 35,024, purity 92.1%, was given by gavage at concentrations of 0 (Mazola* oil), 0.1, 0.2, 0.3, or 0.4 mg/kg/day to 24-25 female Sprague-Dawley rats/group during days 6 through 15 of gestation. Treatment related mortality (6/25), lower body weights and lower food consumption were observed in the high dose group. Maternal NOEL = 0.3 mg/kg/day. Incidence of retarded fetal ossification (sternebrae and pelvis variations) increased and lower fetal weights were observed for the high dose group. No other fetal abnormalities were reported. Developmental NOEL = 0.3 mg/kg/day. ACCEPTABLE, WITH NO ADVERSE EFFECTS. (Kishiyama and Gee, 6/12/92).

017 016843, -44 (EPA, Environmental Health Effects Research Series Report, EPA-600/1-78-003, January 1978.) Summary only. Groups of 10 pregnant rats were exposed to aerosols of phorate from day 7 through 14 of gestation at 0.15, 0.40 or 1.94 mg/m^3; 50% mortality at high dose; no teratogenic effect was noted. Schreider, 3/27/85.

029 034580, "Teratology Study in Rats [with] Thimet Phorate: Final Report", (Litton Bionetics, 5/78, revised 3/79, LBI Project No. 20819). Technical grade Phorate, Lot# W-70513-4844-2, 91.7% pure was given by oral gavage to groups of 24 CRL Rats at 0, 0.125, 0.25 or 0.50 mg/kg/day (based on day 6 body weight) from days 6-15 of gestation. Maternal mortality was 7 of 25 in the high dose group (some due to intubation errors), 1 of 25 in the low dose group, and 0/25 in controls. Maternal NOEL = 0.25 mg/kg (mortality); Developmental NOEL = 0.25 mg/kg **(enlarged hearts)**. The study was initially reviewed as unacceptable (individual body weights, food consumption, and number of corpora lutea not reported; skeletal findings not tabulated; resorptions not classified as early or late; and no analysis of dosing solutions), but upgradeable. **A possible adverse effect (enlarged fetal hearts) was noted**. Upon review, the status of the study remained unacceptable but upgradeable, and the finding of a possible adverse effect was reversed based on an association between maternal toxicity and enlarged fetal hearts (J. Schreider, 3/27/85 and J. Remsen (Gee), 11/1/85). In a CDFA Response dated May 5, 1988, the requirements for considering upgrading the study status were reduced to submission of the protocol and records of dosing preparations along with retrospective analyses of the dosing solution, all of which were satisfied in CDFA record no. 075269. The study was upgraded to acceptable status with reinstatement of the original finding of a possible adverse effect pending review of the pathology and criteria used to determine enlarged fetal heart (G. Chernoff, 8/25/89). After consideration of the review submitted in CDFA record no. 090085, the

finding of a **POSSIBLE ADVERSE HEALTH EFFECT** remains, and the study status is downgraded to UNACCEPTABLE but upgradeable pending favorable review of documentation on the possible intercurrent disease problem (respiratory infection) and relative inexperience of the investigators (G. Chernoff, 12/27/89).

EPA-liner: Guideline. Teratogenic NOEL > 0.5 mg/kg (HDT); fetotoxic NOEL = 0.25 mg/kg (enlarged hearts), maternal NOEL = 0.25 mg/kg/day.

004 928015 Less complete version of 034580.

048 075269 Supplemental information for 034580, retrospective analysis of the dosing solutions.

049 090085 Supplemental information for 034580, review of enlarged fetal hearts and maternal toxicity data.

Summary: The two studies above used the same strain of rat and the same vehicle, corn oil, but were conducted at different laboratories approximately 10 years apart. The doses used were in the same range. The earlier study, Record no. 034580, has undergone several reviews with differing opinions. The latest evaluation by Dr. G. Chernoff requested some additional information, which has not been submitted to date. Since the study performed at Litton has merit, the possible adverse effect of enlarged hearts remains pending receipt of the requested information. In addition, the NOEL's for the possible developmental effect, 0.25 mg/kg/day, and for maternal effects (mortality, tremors, etc.) of 0.3 mg/kg/day, are approximately the same. No effect on the fetal heart was reported in Record No. 089065. A document from U.S. EPA dated 1/18/89 indicates a LEL of 0.5 mg/kg for enlarged hearts for 034580. Gee, 6/12/92.

TERATOLOGY, RABBIT

038 058865 "A Teratology Study with Phorate in Rabbits." (Biodynamics Inc, 4-6-87) Phorate, lot AC4870-110, 92.1%, was administered by gavage to mated New Zealand White rabbits at 0 (corn oil), 0.15, 0.5, 0.9 or 1.2 mg/kg/day on days 6-18 of gestation, 20/group. Animals were sacrificed on day 30 of gestation. Maternal NOEL = 0.15 mg/kg/day (death, reduced body weight gain, reduced food consumption, staining of fur.) Developmental NOEL >= 1.2 mg/kg/day, no treatment related effects. ACCEPTABLE.** Shimer and Gee, 2/29/88.

029 034582 "A Teratology Study with AC 35,024 in Rabbits." (WIL Research Labs, 5/7/84, project No. WIL-35008) Phorate, 91.7%, lot W-70513-4344; given by oral intubation days 6 through 18 of pregnancy to 18 rabbits per group at 0, 0.3, 0.6, or 0.9 mg/kg/day; 5 deaths in high dose group, UNACCEPTABLE (dose preparation problem first five days of treatment so 50% of target, no stability information,) no evidence of terata; sys NOEL = 0.6 mg/kg/day (nominal) (mortality, decreased gravid uterine weights), nominal developmental NOEL = 0.6 mg/kg/day (resorptions). J. Remsen (Gee), 11/1/85.

029 034581 Pilot study for 034582.

Summary: The results reported in the two studies agree rather well for the maternal NOEL considering the problems with dosing preparation in the study conducted at WIL. Gee, 3/1/88.

MUTAGENICITY, GNMU

039 058866 "Mutagenicity Testing of Technical Thimet Phorate in the Ames Bacterial Test." (American Cyanamid Research and Development Dept., 4-13-78) Technical Thimet Phorate, CL 35,024, lot AG 59,673 drum no. 1 (no purity stated), was tested for mutagenicity by the disc test and by plate incorporation with and without rat liver metabolic activation. *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP-2 uvrA- were used. Test levels were 1000 ug/disc and 10, 100 or 1000 ug/plate. No increase in revertants noted. UNACCEPTABLE**.** Single plate per

concentration, should have 5 concentrations, the maximum concentration should be 5 mg/plate or solubility described. No mention of cytotoxicity. Shimer and Gee, 2/25/88.

039 058867 "Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells with and without Metabolic Activation." (Sitek Research Laboratories, 8-8-85) Phorate, AC 35,024, lot AC 4870-110, 92.1%, was tested in the CHO HGPRT gene mutation assay. With S9 mix for activation, cells were treated at 100, 80, 50, 40 or 30 nl/ml. Without activation cells were treated at 16, 14, 12, 10 or 5 nl/ml, 5 hours exposure, eight days for expression. DMBA and EMS were used for controls. Triplicate cultures were used at each dose level. No increase in mutation frequency. ACCEPTABLE.** No analysis of dosing solution. Shimer and Gee 2/25/88.

004 928016 "Mutagenicity Testing of Technical Thimet Phorate Following the Addition of a Mercaptan Scavenger in the Ames Bacterial Test." (American Cyanamid, 4/13/78). *Salmonella* strains TA1535, TA1537, TA98 and TA100, with and without activation, phorate, no purity stated; single plate, tested at 0, 10, 100 or 1000 ug/plate; also tested *E. coli* strain WP-2 urvA__; UNACCEPTABLE (missing page 202, single value only); no evidence for mutagenicity. J. Schreider, 3/27/85 and J. Remsen (Gee), 10/30/85.

030 034583 Duplicate of 928016.

035 052317 "Microbiological Assays, in: Evaluation of Selected Pesticides as Chemical Mutagens "*in vitro*" and "*in vivo*" Studies." (SRI, 5/77, PB-268 647, LSU-3493) _*Salmonella* strains TA1535, TA1537, TA1538 and TA100 (no TA98), with and without mouse (not clear if mouse or rat) liver activation; one plate, one trial; tested at 0, 1, 5, 10, 50, 100, 500 or 1000 ug/plate; UNACCEPTABLE (no purity of test article, no justification of maximum concentration, activation source unclear); no evidence for increase in reversion rate is reported. Marginal suggestion of cytotoxicity in TA100, +S9. J. Gee, 2/24/87 and 2/26/88.

042 060150 Addendum to 035 052317. An exact duplicate of text is presented and some hand written lab book pages containing plate counts. It appears 2 plates were done for strains TA1535, TA1537 and TA1538, one plate for TA100.

MUTAGENICITY, CHROMOSOME

039 058868 "Chromosomal Aberrations in vivo in Mammalian Bone Marrow Cells on AC 35 024 Lot AC4870-110 Cyanamid Protocol No. 980-85-162." (Litton Bionetics Inc., 12-24-85) AC 35,024, 92.1%, was administered to Sprague-Dawley rats, 5/sex/time point, by intraperitoneal injection at 2.50, 1.25, 0.25, and 0 mg/kg for males and 1.25, 0.63 and 0.13 mg/kg for females. There were excessive deaths in high dose males so another high dose group was initiated at 1.75 mg/kg. Animals were sacrificed at 6, 18 and 30 hours after dosing. Fifty metaphase spreads per animal were scored. No increase in chromosomal aberrations were noted. ACCEPTABLE.** Shimer and Gee, 2/25/88.

017 016430, 016840, -42 Summary of dominant lethal study, 1977. No data. Results reported as negative.

006 034037 Two-line summary, no data. for dominant lethal study.

035 052286 "Dominant Lethal Test in the Mouse, in: Evaluation of Selected Pesticides as Chemical Mutagens *"in vitro*" and "*in vivo*" Studies." (SRI, 5/77, PB 268 647, Report no. LSU-3493.) Phorate, lot MC85, no purity stated; ICR/SIM mice, 20 males per group, fed at 0, 5, 10 or 20 mg/kg of diet (20 ppm) for 7 weeks, then mated 1:2 females for 8 weekly periods; [dose estimated by reviewer as 3 mg/kg/day]; no evidence for a dominant lethal effect; UNACCEPTABLE (no evidence of approach to MTD reported, no analysis of diet.) Document 042 60282, addendum to 52286, states test article was technical grade, 85% pure, 20 mg/kg was MTD based on a 2-week feeding study and provides

individual mating data. Submission improves usefulness of the study but does not upgrade it to acceptable. J. Gee, 2/24/87 and 2/26/88.

MUTAGENICITY, DNA/OTHER

035 052305 "Microbiological Assays, in: Evaluation of Selected Pesticides as Chemical Mutagens "in vitro" and "in vivo" Studies." (SRI, 5/77, PB-268 647, LSU-3493) Phorate, technical, no purity stated, lot MC85; *Saccharomyces cerevisiae* strain D3, diploid, for mitotic recombination; tested at 0 or 5% v/v, with and without activation (not clear if mouse or rat); incubation for 4 hours, then plated; no evidence for genotoxic effect; UNACCEPTABLE (need detailed protocol including number of plates, cytotoxicity data with justification of concentration selected - did not demonstrate the target 50% growth inhibition, not clear if rat or mouse liver activation.) Document 042 60282 contains the statement that lot MC85 was 85% active ingredient. Gee, 2/24/87 and 3/1/88.

035 052285 "Microbiological Assays, in: Evaluation of Selected Pesticides as Chemical Mutagens "in vitro" and "in vivo" Studies." (SRI, 5/77, PB-268 647, LSU-3493) Phorate technical, no purity stated, lot MC85; *Escherichia coli* strains W3110 and p3478, and Bacillus subtilis strains H17 and M45; tested without activation at 0 or 1 mg/6 mm disk; no growth inhibition for any strain, therefore, a "no test"; UNACCEPTABLE (no activation, no justification for amount used, stated that three trials were run but only single value reported). Document 042 60282 contains the statement that lot MC85 was 85% active ingredient. Gee, 2/24/87 and 3/1/88.

**035 052319 and 042 060284 "Mammalian *In vitro* Unscheduled DNA Synthesis Assays, in: Evaluation of Selected Pesticides as Chemical Mutagens "*in vitro*" and "*in vivo*" Studies." (SRI, 5/77, PB-268 647, LSU-3493) Phorate technical, no purity stated; WI-38 human diploid fibroblasts (passage number not stated); incubated 3 hours without activation at 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} M, 6 replicates; incubated 1 hour with mouse liver activation at 10^{-5}, 10^{-4} and 10^{-3} M, in triplicate; DNA extracted by a modification of the PCA-hydrolysis method; incorporation of [^{3}H]-thymidine into DNA measured by liquid scintillation spectrometry and the results expressed as dpm/ug DNA; no increase in UDS reported; initially reviewed as unacceptable but possibly upgradeable based on no purity of test article, protocol converting cpm to dpm, amount of DNA per flask of cells.) With submission of #60284, protocols and passage information, the study is upgraded to ACCEPTABLE status. Gee, 2/24/87 and 2/29/88.

Documents on file with Pesticide Registration indicate a new study on DNA repair is planned. Gee, 2/29/88.

NEUROTOXICITY

002 928025 "Thimet Systemic Insecticide: Demyelination Studies in White Leghorn Hens." (American Cyanamid, 10/4/65, no. 65-107.) Phorate, no purity stated; given orally to 12 controls or 6 per test group, at 0, 20, 40 or 80 ppm; UNACCEPTABLE (dose selection with doses based on 1/4 to 1/16 the LD50 - not high enough, use of feed as the route of administration, test article not described.) J. Schreider, 3/25/85.

004 928026 Duplicate of 928025.

**031 034579 "42-Day Neurotoxicity Study with Phorate in Mature White Leghorn Chickens." (BIO LIFE, 9/18/84) Phorate, 89.5%; given orally at 0 or 14.7 mg/kg, protected; 15 hens in control group and 50 in test group; 23 were re-dosed at day 21 with 13/23 dying within 24 hours and 10 recovering; hens were older than recommended at start; no evidence of delayed neuropathy. ACCEPTABLE. J. Remsen (Gee), 10/31/85.